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Department of Health and Human Services

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice of Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth eight actions to be taken by the Director, National Institutes of Health (NIH), under the May 7, 1986, NIH Guidelines for Research Involving Recombinant DNA Molecules (51 FR 16958).

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities (ORDA), Office of Science Policy and Legislation, National Institutes of Health, building 31, room 4B11, Bethesda, Maryland 20892, (301) 496–9838.

SUPPLEMENTARY INFORMATION: Today eight actions are being promulgated under the NIH Guidelines for Research Involving Recombinant DNA Molecules. These eight proposed actions were published for comment in the **Federal Register** of July 2, 1991 (56 FR 30398), September 3, 1991 (56 FR 43686), November 4, 1991 (56 FR 56415), and January 3, 1992 (57 FR 316) reviewed and recommended for approval by the NIH Recombinant DNA Advisory Committee (RAC) at its meeting on February 10–11, 1992.

I. Background Information and Decisions on Actions Under the NIH Guidelines

A. Addition of Appendix D–XXIV to the NIH Guidelines

In a letter dated October 18, 1991, Dr. Gary J. Nabel of the University of Michigan Medical School, Ann Arbor, Michigan, indicated his intention to submit a human gene therapy protocol to the Human Gene Therapy Subcommittee (HGTS) and the RAC for formal review and approval. The title of this protocol is: "Immunotherapy of Malignancy by In Vivo Gene Transfer into Tumors." This request was published for comment in the **Federal Register** on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the Human Gene Therapy Subcommittee (HGTS) meeting on November 21–22, 1991. Provisional approval was given with the following conditions: (i) Amend consent form regarding possibility of sensitization to the human antigen; (ii) expand the clinical protocol regarding the number of biopsies; (iii) make available the nucleotide sequence analysis of the total construct of the vector; and (iv) provide clarification concerning the status of DNA integration in tumor cells. Dr. Nabel submitted the requested documentation to ORDA. The protocol was then forwarded to the RAC for consideration during the February 10–11, 1992, meeting. This request was published for comment in the **Federal Register** on January 3, 1992 (57 FR 316).

During the meeting on February 10, 1992, the RAC met to review the protocol and recommendations from the HGTS. A modification was requested to the patient's informed consent document in the Description of Treatment or Procedures to be Undertaken section. The revised wording in the consent form is to read as follows:

"By using techniques in the laboratory it is now possible to prepare large amounts of human DNA or genetic material and bacteria. This DNA will be mixed with fat bodies called liposomes, and we plan to transport the mixture into your tumor by a bacterial carrier or delivery system.

Also included in this package is a separate bacterial gene which helps us trace the location of the DNA liposome mixture. Once introduced into the tumor the DNA produces a protein which stimulates tissue rejection. This protein, known as HLA–B7, causes the cells which will contain it to be recognized as a foreign enemy by your immune system.

The purpose of our study is to determine whether this treatment will induce the cells of your immune system, known as lymphocytes, to attack and kill your tumor."

The RAC, by a vote of 13 in favor, 0 opposed, and 1 abstention, approved the protocol. The following section may be added to Appendix D:

Appendix D–XXIV

Dr. Gary J. Nabel of the University of Michigan Medical School, Ann Arbor, Michigan, can conduct gene therapy experiments on twelve patients with melanoma or adenocarcinoma. The patient population will be limited to adults over the age of 18 and female patients must be postmenopausal or have undergone tubal ligation or orchiectomy. The patient's immune response will be stimulated by the introduction of a gene encoding for a Class I MHC protein, HLA–B7, in order to enhance tumor regression. DNA/liposome-mediated transfection techniques will be used to directly transfer the foreign gene into tumor cells. HLA–B7 expression will be confirmed in vivo and the immune response stimulated by the expression of this antigen will be characterized.

These experiments will be analyzed for their efficacy in treating cancer.

I accept this recommendation and appendix D–XXIV of the NIH Guidelines will be added accordingly.

B. Addition of Appendix D–XXV to the NIH Guidelines

In a letter dated October 10, 1991, Dr. Kenneth Cornetta of Indiana University, Indianapolis, Indiana, indicated his intention to submit a human gene transfer protocol to the HGTS and the RAC for formal review and approval. The title of this protocol is: "Retroviral-Mediated Gene Transfer of Bone Marrow Cells During Autologous Bone Marrow Transplantation for Acute Leukemia." This request was published for comment in the **Federal Register** on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the HGTS meeting on November 21–22, 1991. Provisional approval was given with the following conditions: (1) Amend the consent form regarding the possible benefit of the introduction of the gene; (ii) amend the consent form regarding compensation to the patient related to the research aspects of the protocol; (iii) demonstrate that the transduced leukemic cells will survive the freezing process; and (iv) add a statistical section that addresses the interpretation of recurrence of disease in labeled bone marrow specimens; it is important to determine how many cells contribute to a relapse. Dr. Cornetta submitted the requested documentation to ORDA. The protocol was then forwarded to the RAC for consideration during the February 10–11, 1992, meeting. The request was published for comment in the **Federal Register** on January 3, 1992 (57 FR 316).

During the meeting on February 11, 1992, the RAC met to review the protocol and recommendations from the HGTS. It was decided that the issues raised by the HGTS had been adequately addressed. The RAC, by a vote of 15 in favor, 1 opposed, and no abstentions, approved the protocol. The following section may be added to appendix D:

Appendix D–XXV

Dr. Kenneth Cornetta of Indiana University, Indianapolis, Indiana, can conduct gene transfer experiments on up to 10 patients with acute myelogenous leukemia (AML) and up to 10 patients with acute lymphocytic leukemia (ALL). The patient population will be limited to persons between 18 and 65 years of age. Using the LNL–6 vector, autologous bone marrow cells will be marked with the neomycin resistance gene. Gene marked and untreated bone marrow cells will be reinfused at the time of bone marrow transplantation. Patients will then be monitored for evidence of the neomycin resistance gene in peripheral blood and bone marrow cells in order to determine whether

relapse of their disease is a result of residual malignant cells remaining in the harvested marrow, or inadequate ablation of the tumor cells by chemotherapeutic agents. Determining the source of relapse may indicate whether or not purging of the bone marrow is a necessary procedure for these leukemia patients. Further studies will be performed in order to determine the percentage of leukemic cells that contain the LNL-6 vector and the clonality of the marked cells.

I accept this recommendation and Appendix D–XXV of the NIH Guidelines will be added accordingly.

C. Addition of Appendix D–XXVI to the NIH Guidelines

In a letter dated October 15, 1991, Dr. James S. Economou of the University of California, Los Angeles, indicated his intention to submit a human gene transfer protocol to the HGTS and the RAC for formal review and approval. The title of this protocol is: "The Treatment of Patients With Metastatic Melanoma and Renal Cell Cancer Using *In Vitro* Expanded and Genetically-Engineered (Neomycin Phosphotransferase) Bulk, CD8(+) and/or CD4(+) Tumor Infiltrating Lymphocytes and Bulk, CD8(+) and/or CD4(+) Peripheral Blood Leukocytes in Combination With Recombinant Interleukin-2 Alone, or with Recombinant Interleukin-2 and Recombinant Alpha Interferon." This request was published for comment in the Federal Register on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the HGTS meeting on November 21–22, 1991. Provisional approval was given with the following conditions: (i) All data concerning vector safety and testing must be submitted; (ii) patient eligibility will be limited to those with at least one lesion that can be biopsied post therapy; (ii) the schedule for the post therapy assessment of cell trafficking is to be added; (iv) develop a statistical section for analysis of cell trafficking; (v) submit proportionality experiments demonstrating the limits of the ability to quantitate differences in ratio of the two vectors; (vi) submit data showing stable integration of the genetic markers in chronic cell cultures; (vii) modify the consent form so that the language concerning biopsies is moved from the biomodulator section to the viral marker section; and (viii) include a stopping rule in the protocol if the *in vivo* trafficking data is uninterpretable. Dr. Economou submitted the requested documentation to ORDA. The protocol was forwarded to the RAC for consideration during the February 10–11, 1992, meeting. The request was published for comment in the Federal Register on January 3, 1992 (57 FR 316).

During the meeting on February 11, 1992, the RAC met to review the protocol and recommendations from the HGTS. It was decided that the issues raised by the HGTS had been adequately addressed. The RAC, by a vote of 15 in favor, 0 opposed and no abstentions, approved the protocol. The following section may be added to appendix D:

Appendix D–XXVI

Dr. James S. Economou of the University of California, Los Angeles, can conduct gene transfer experiments on 20 patients with metastatic melanoma and 20 patients with renal cell carcinoma. These patients will be treated with various combinations of tumor-infiltrating lymphocytes and peripheral blood leukocytes, including CD8 and CD4 subsets of both types of cells. These effector cell populations will be given in combination with interleukin-2 (IL–2) in the melanoma patients and IL–2 plus alpha interferon in the renal cell carcinoma patients. The effector cells will be transduced with the neomycin resistance gene using either the LNL6 or G1N retroviral vectors. This "genetic marking" of the tumor-infiltrating lymphocytes and peripheral blood lymphocytes is designed to answer questions about the trafficking of these cells, their localization to tumors, and their *in vivo* lifespan.

I accept this recommendation and Appendix D–XXVI of the *NIH Guidelines* will be added accordingly.

D. Addition of Appendix D–XXVII to the NIH Guidelines

In a letter dated October 8, 1991, Dr. Philip D. Greenberg of the University of Washington, Seattle, Washington, indicated his intention to submit a human gene therapy protocol to the HGTS and the RAC for formal review and approval. The title of this protocol is: "A Phase I/II Study of Cellular Adoptive Immunotherapy Using Genetically Modified CD8 + HIV-Specific T Cells for HIV-Seropositive Patients Undergoing Allogeneic Bone Marrow Transplant." This request was published for comment in the Federal Register on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the HGTS meeting on November 21–22, 1991. Approval was given with the following requested changes in the patient consent form: (i) Reword the language regarding unforeseen problems; (ii) reword the language concerning the costs associated with the research aspects of the protocol and billing to the patients; (iii) clearly distinguish between the therapy and the gene modification portions of the protocol; (iv) use less technical terminology throughout the document; and (v) provide hard copies of the helper-virus assay and vector testing slides presented during the HGTS meeting. Dr. Greenberg submitted the requested documentation to ORDA. The protocol was forwarded to the RAC for consideration during the February 10–11, 1992, meeting. The request was published for comment in the Federal Register on January 3, 1992 (57 FR 316).

During the meeting on February 11, 1992, the RAC met to review the protocol and recommendations from the HGTS. It was decided that the issues raised by the HGTS had been adequately addressed. The RAC, by a vote of 16 in favor, 0 opposed, and no abstentions, approved the protocol. The following section may be added to appendix D.

Appendix D–XXVII

Dr. Philip D. Greenberg of the University of Washington, Seattle, Washington, can conduct gene transfer experiments on up to 15 HIV seropositive patients undergoing allogeneic bone marrow transplantation for non-Hodgkin's lymphoma to evaluate the safety and efficacy of HIV-specific cytotoxic T lymphocyte (CTL) therapy. CTL will be transduced with a retroviral vector (HyTK) encoding a gene that is a fusion product of the hygromycin phosphotransferase gene (HPH) and the herpes virus thymidine kinase (HSV–TK) gene. This vector will deliver both a marker gene and a suicide gene in these T cell clones in the event that patients develop side effects as a consequence of CTL therapy. Data will be correlated over time, looking at multiple parameters of HIV disease activity. The objectives of these studies include evaluating the safety and toxicity of CTL therapy, determining the duration of *in vivo* survival of HIV-specific CTL clones, and determining if ganciclovir therapy can eradicate genetically modified, adoptively transferred CTL cells.

I accept this recommendation and appendix D–XXVII of the NIH Guidelines will be added accordingly.

E. Amendment to Appendix D–XV of the NIH Guidelines

In a letter dated December 20, 1991, Drs. R. Michael Blaese and W. French Anderson of the National Institutes of Health, Bethesda, Maryland, requested an action item concerning a major amendment to the protocol entitled, "Treatment of Severe Combined Immunodeficiency Disease (SCID) due to Adenosine Deaminase (ADA) Deficiency With Autologous Lymphocytes Transduced With a Human ADA Gene." This protocol was originally approved by the RAC at its meeting on July 31, 1990, and approved by the Director, NIH, published in the Federal Register on September 12, 1990 (55 FR 37565).

The requested amendment would use CD–34+ cells (the peripheral blood stem cell fraction) transduced with the gene coding for adenosine deaminase (ADA) as a supplemental therapy for patients with ADA deficiency. The request was published for comment in the **Federal Register** on January 3, 1992 (57 FR 316), and a correction notice published in the **Federal Register** on July 18, 1991 (56 FR 33174).

During the meeting on February 10–11, 1992, the RAC met to review this amendment to the protocol. The RAC, by a vote of 11 in favor, 3 opposed and 2 abstentions, approved the amendment to the protocol. The following section may be appended to appendix D–XV:

Appendix D–XV

In addition to the conditions outlined in the initial approval, patients may be given a supplement of CD 34+ enriched peripheral blood lymphocytes (PBL) which have been placed in culture conditions that favor progenitor cell growth. This enriched population of cells will be transduced with the retroviral vector, G1NaSvAd. G1NaSvAd is similar to LASN, yet distinguishable by the polymerase chain reaction (PCR). LASN has been used to transduce peripheral blood T lymphocytes with the ADA gene. Lymphocytes and myeloid cells will be isolated from patients over time and assayed for the presence of the LASN or G1NaSvAd vectors. The primary objectives of this protocol are to transduce CD34+ peripheral blood cells with the adenosine deaminase gene, administer these cells to patients, and determine if such cells can differentiate into lymphoid and myeloid cells in vivo. There is a potential for benefit to the patients in that these hematopoietic progenitor cells may survive longer, and divide to yield a broader range of gene-corrected cells.

I accept this recommendation and appendix D–XV of the NIH Guidelines will be amended accordingly.

F. Amendment to Sections III–A and IV–C of the NIH Guidelines Regarding Notice of Meeting and Proposed Actions; Amendment to Introduction, Parts II, and V of the Points to Consider Regarding Review by the Human Gene Therapy Subcommittee

During the HGTS meeting on July 30–31, 1991, a Working Group on the Future Role of the Recombinant DNA Advisory Committee was established to prepare a report about the feasibility of merging the HGTS and the RAC. This request was published for comment in the **Federal Register** on November 7, 1991 (56 FR 56415).

The HGTS received a report from this working group during its meeting on November 21–22, 1991, which recommended that: (i) All eligible HGTS members be added to the RAC as full voting members; or (ii) all of the HGTS members be added to the RAC as non-voting members; or (iii) joint meetings would be held in which the HGTS would vote on the proposed action first, followed by the full RAC. During the meeting, the following motion passed by a vote of 11 in favor, 2 opposed, and no abstentions:

We move to recommend to the Recombinant DNA Advisory Committee, that its subcommittee, the Human Gene Therapy Subcommittee, be merged into the parent committee. The number of meetings per year of the Recombinant DNA Advisory Committee would increase to four per year. There would be a transition period of one year in which the Recombinant DNA Advisory Committee would begin to review proposed actions as the sole review group. The following provisions would apply: (i) The Human Gene Therapy Subcommittee would codify a set of guidelines for shortening the review process, and (ii) the eligible members of the Human Gene Therapy Subcommittee would be brought onto the Recombinant DNA Advisory Committee as full voting members in keeping with the nomination process for Federal Advisory Committees.

The HGTS forwarded the proposal to the RAC for consideration during the February 10–11, 1992, meeting.

In a letter dated December 23, 1991, Dr. Nelson Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Maryland, stated that amendments will need to be made to the NIH Guidelines in sections III–A and IV–C and to the Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects in the Introduction, Parts II, and V, in the event that the HGTS recommendations are accepted. If the recommendation on having more meeting dates to accommodate the expected increase in human gene transfer/therapy protocols is accepted, the Notices of Meeting and Proposed Actions will need to be changed from thirty days to fifteen days to allow expedited review. Changes are required in Sections III–A and IV–C of the NIH Guidelines. If the recommendation to have the HGTS merge into the parent committee is approved, all references to the HGTS will need to be deleted in the Points to Consider, in the Introduction, and Parts II, and V.

These requests were published for comment in the **Federal Register** on January 3, 1992 (57 FR 316).

During the meeting on February 10, 1992, the RAC met to review the requests of the HGTS and Dr. Wivel. The RAC, by a vote of 14 in favor, 0 opposed and no abstentions, approved: (1) To eliminate review of the human gene transfer/therapy protocols by the HGTS; this established sole review of the protocols by the RAC; and (2) to change all references to thirty day Notice of Meeting and Proposed Actions to fifteen days. The RAC also recommended increasing the number of times the committee meets from three times a year to four times a year.

The following sections will be amended in the NIH Guidelines: Sections III–A, IV–C–1–b–(1), section IV–C–2, section IV–C–3–b–(1), section IV–C–3–b–(2)). The amended sections will read:

Section III–A. Experiments That Require RAC Review and NIH and IBC Approval Before Initiation

Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH, the publication of the proposal in the **Federal Register** for 15 days of comment, review by the RAC, and specific approval by NIH. The containment conditions for such experiments will be recommended by the RAC and set by NIH at the time of approval. Such experiments also require * * *.

Section IV–C–1–b–(1). Major Actions. To execute major actions, the Director, NIH, must seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the agenda of the RAC meeting citing the major actions will be published in the **Federal Register** at least 15 days before the meeting, and the Director, NIH, will also publish the proposed actions in the **Federal Register** for comment at least 15 days before the meeting.

In addition, the Director's proposed decision, at his/her discretion, may be published in the **Federal Register** for 15 days of comment before final action is taken. The Director's final decision * * *.

Section IV–C–2. Recombinant DNA Advisory Committee. * * * All meetings of the RAC will be announced in the **Federal Register**, including tentative agenda items, 15 days in advance of the meeting with final agendas, if modified, available at least 72 hours before the meeting. No item defined as * * *.

Section IV–C–3–b–(1). Announcements of RAC meetings and agendas at least 15 days in advance; NOTE—If the agenda * * *.

Section IV–C–3–b–(2). Proposed major actions of the type falling under Section IV–C–1–b–(1) at least 15 days prior to the RAC meeting at which they will be considered; and

The following sections will be amended to the Points to Consider: The Introduction, Parts II, and V. This document was published in the **Federal Register** on March 1, 1990 (55 FR 7437), amended September 12, 1990 (55 FR 37565), and amended July 18, 1991 (56 FR 33174). The amended sections will read:

Introduction. (1) * * * RAC consideration of each proposal will be on a case-by-case basis and will follow publication of a precis of the proposal in the **Federal Register**, and an opportunity for public comment. RAC's recommendation on each proposal will be

forwarded to the NIH Director for a decision which will then be published in the **Federal Register.**

Introduction. (4) * * * The IRB and IBC may, at their discretion, condition their approval on further specific deliberation by the RAC. Consideration of proposals by the RAC may proceed simultaneously with review by any other Federal agencies provided that the RAC is notified of the simultaneous review. Meetings of the RAC will be open to the public except where trade secrets or proprietary information would be disclosed. The committee * * *.

Introduction. (6) * * * Part III summarized other requested documentation that will assist the RAC in their review of the proposals. Part IV specified reporting requirements.

Introduction. (7) The RAC will not at present entertain proposals for germ line alterations * * *.

Introduction. (9) In their evaluation of proposals involving the transfer of recombinant DNA into human subjects, the RAC will consider whether the design * * *. Accordingly, this document requests information that will enable the RAC to assess the possibility that the proposed experiments will inadvertently affect reproductive cells or lead to infection of other people (e.g., treatment of personnel or relatives).

Introduction. (10) In recognition of the social concern that surrounds the subject of gene transfer, the RAC will cooperate with other groups * * *.

Introduction. (12) * * * Investigators submitting proposals that employ essentially the same vector systems (or with minor variations), and/or that are based on the same preclinical testing as proposals previously reviewed by the RAC, may refer to preceding documents without having to rewrite such materials.

Part II. Special Issues. Although the following issues are beyond the normal purview of local IRBs, the RAC requests that the investigators respond to questions A and B below.

Part V. Minor Modifications. A minor change in a protocol approved by the RAC is a change that does not significantly alter the basic design of a protocol and that does not increase risk to the subjects. If the change has been approved by the relevant IRB and IBC, then the Chair of the RAC may give approval. It is expected that the Chair will consult with one or more members of the committee, as necessary. The Chair will report on any such approvals at the next regularly scheduled meeting of RAC.

I accept this recommendation to amend accordingly the NIH Guidelines in sections III–A and IV–C and to amend the Points to Consider in the Introduction, Parts II, and V.

G. Amendment to Appendices B–I–B–1 and B–I–B–2 of the NIH Guidelines regarding the Bacterial Order, Actinomycetales

In a written request dated April 15, 1991, Dr. Diane O. Fleming, representing the Mid-Atlantic Biological Safety Association, requested that only pathogenic genera and species of the bacterial order, Actinomycetales, be included in Appendix B–I–B–1 of the NIH Guidelines.

It was proposed that the following pathogens be included in the list of Bacterial Agents in Appendix B–I–B–1 of the NIH Guidelines as follows:

Actinomadura madurae, Actinomadura pelletieri, Actinomyces bovis, Actinomyces israelii, Nocardia asteroides, Nocardia brasiliensis

In appendix B–I–B–2, the entry under Actinomycetes would be deleted.

This request was reviewed at the RAC meeting on May 30–31, 1991. Following a discussion there was agreement that Actinomyces should be removed from the list of fungi and reclassified as bacteria. There was disagreement, however, about the number of species to be listed as pathogens. Reviewers and committee members expressed concern that the number of possible pathogens may be larger than the six species proposed for inclusion. The RAC requested that Dr. Fleming consult with leading experts on Actinomycetales and develop a revised and expanded list of potential pathogens to be reviewed at the RAC meeting on October 7–8, 1991. This request was published for comment in the **Federal Register** on September 3, 1991 (56 FR 43686).

A second list of potential pathogens was submitted to the RAC. This included 63 organisms, a number that was reduced to 56 by clarification of taxonomic names and was reviewed by Dr. Lechevalier at Rutgers University, Dr. Blaine Beaman of the University of California at Davis, and Drs. Michael McNeil and Richard Knudsen at the Centers for Disease Control (CDC). Drs. McNeil and Knudsen presented a synopsis of their review at the RAC meeting of October 7–8, 1991.

During the October 7–8, 1991, RAC meeting, a motion was passed by a vote of 19 in favor, 0 opposed, and no abstentions to create an ad hoc working group within the RAC, plus outside consultants, to provide an amended list of pathogens.

On November 13, 1991, the RAC Working Group on Actinomycetales held a telephone conference call for the purpose of proposing a list of pathogens. Drs. B. Murray, D. Fleming, D. Krogstad, and M. Schaechter participated. Originally, a list of 19 organisms was developed; this included both the proven pathogens identified by the CDC and the suspected pathogens identified by the CDC that were also part of risk group 2 (BL–2) in the German classification, *"Klassifizierung Der Bakterien Nach Den Im Ungang Mit Ihnen Auftretenden Gefahren."* Thesed organisms are as follows:

Actinomadura madurae, Actinomadura pelletieri, Amycolata autotrophica, Dematophilus congolensis, Gordona bronchialis, Gordona sputi, Nocardia asteroides, Nocardia brasiliensis, Nocardia otitidiscaviarum, Nocardia farcinica, Nocardia nova, Nocardia transvalensis, Nocardiopsis dassonvillei, Rhodococcus equi, Rhodococcus aichiensis, Rhodococcus chubuensis, Rhodococcus rhodochrous, Rhodococcus ruber, Streptomyces Somaliensis.

Alternatively, a list of organisms representing only proven pathogens, as established by the CDC, would read as follows:

Amycolata autotrophica, Dermatophilus congolensis, Nocardia asteroides, Nocardia brasiliensis, Nocardia otitidiscaviarum, Nocardia transvalensis, Rhodococcus equi.

The request was published for comment in the **Federal Register** on January 3, 1992 (57 FR 316).

During the meeting on February 10, 1992, the RAC discussed the recommendations of the Working Group on Actinomycetales. The RAC, by a vote of 13 in favor, 0 opposed, and no abstentions, accepted the working group's recommendation to adopt the CDC classification of organisms with proven pathogenicity.

The following proven pathogens of the bacterial order, Actinomycetales, will be added to Apendix B–I–B–1, Bacterial Agents:

"Amycolata autotrophica, Dermatophilus congolensis, Nocardia asteroides, Nocardia brasiliensis, Nocardia otitidiscaviarum, Nocardia transvalensis, Rhodococcus equi."

The following organisms will be deleted from appendix B–I–B–2, Fungal Agents:

"Actinomycetes (including Nocardia species, Actinomyces species, and Arachnia propionica)[2]."

I accept this recommendation and Appendices B–I–B–1 and B–I–B–2 of the NIH Guidelines will be amended accordingly.

H. Amend Appendices B–I–C–1and B–I–B–1 in the NIH Guidelines Regarding Mycobacterium Avium

In a letter dated December 18, 1991, Dr. William R. Jacobs, Jr., of the Albert Einstein College of Medicine, Bronx, New York, requested a lowering of the classification Mycobacterium avium from a Class III bacterial agent to a Class II bacterial agent. M. avium would move from Appendix B–I–C–1 to Appendix B–I–B–1 in the NIH

Guidelines. The request was published for comment in the Federal Register on January 3, 1992 (57 FR 316).

During the meeting on February 11, 1992, the RAC met to review this request. The basis of this request resides in the fact that CDC/NIH biosafety guidelines, that were published in 1984, recommended biosafety level 2 practices for M. avium. M. avium is ubiquitous in nature, a common contaminant in the soil, and there is no evidence that direct transmission occurs between humans. The RAC, by a vote of 14 in favor, 0 opposed, and no abstentions, approved the lowering of the classification of Mycobacterium avium from a Class III bacterial agent to a Class II bacterial agent. M. avium would move from Appendix B–I–C–1 to Appendix B–I–B–1 in the NIH Guidelines.

I accept this recommendation and Appendices B–I–C–1 and B–I–B–1 of the NIH Guidelines will be amended accordingly.

II. Summary of Actions

A. Addition of Appendix D–XXIV to the NIH Guidelines

The following section is added to appendix D:

Appendix D–XXIV

Dr. Gary J. Nabel of the University of Michigan Medical School, Ann Arbor, Michigan, can conduct gene therapy experiments on twelve patients with melanoma or adenocarcinoma. Patient population will be limited to adults over the age of 18 and female patients must be postmenopausal or have undergone tubal ligation or orchiectomy. The patient's immune response will be stimulated by the introduction of a gene encoding for a Class I MHC protein, HLA–B7, in order to enhance tumor regression. DNA/liposome-medicatd transfection techniques will be used to directly transfer this foreign gene into tumor cells. HLA–B7 expression will be confirmed in vivo, and the immune response stimulated by the expression of this antigen will be characterized. These experiments will be analyzed for their efficacy in treating cancer.

B. Addition of Appendix D–XXV to the NIH Guidelines

The following section is added to appendix D:

Appendix D–XXV

Dr. Kenneth Cornetta of Indiana University, Indianapolis, Indiana, can conduct gene transfer experiments on up to 10 patients with acute myelogenous leukemia (AML) and up to 10 patients with acute lymphocytic leukemia (ALL). The patient population will be limited to persons between 18 and 65 years of age. Using the LNL–6 vector, autologous bone marrow cells will be marked with the neomycin resistance gene. Gene marked and untreated bone marrow cells will be reinfused at the time of bone marrow transplantation. Patients will then be monitored for evidence of the neomycin resistance gene in peripheral blood and bone marrow cells in order to determine whether relapse of their disease is a result of residual malignant cells remaining in the harvested marrow or inadequate ablation of the tumor cells by chemotherapeutic agents. Determining the source of relapse may indicate whether or not purging of the bone marrow is a necessary procedure for these leukemia patients. Further studies will be performed in order to determine the percentage of leukemic cells that contain the LNL–6 vector and the clonality of marked cells.

C. Addition of Appendix D–XXVI to the NIH Guidelines

The following section is added to appendix D:

Appendix D–XXVI

Dr. James S. Economou of the University of California, Los Angeles, can conduct gene transfer experiments on 20 patients and with metastatic melanoma and 20 patients with renal cell carcinoma. These patients will be treated with various combinations of tumor-infiltrating lymphocytes and peripheral blood leukocytes, including CD8 and CD4 subsets of both types of cells. These effector cell populations will be given in combination with interleukin-2 (IL–2) in the melanoma patients and IL–2 plus alpha interferon in the renal cell carcinoma patients. The effector cells will be transduced with the neomycin resistance gene using either the LNL6 or G1N retroviral vectors. This "genetic marking" of the tumor-infiltrating lymphocytes and peripheral blood lymphocytes is designed to answer questions about the trafficking of these cells, their localization to tumors, and their *in vivo* lifespan.

D. Addition of Appendix D–XXVII to the NIH Guidelines

The following section is added to appendix D:

Appendix D–XXVII

Dr. Philip D. Greenberg of the University of Washington, Seattle, Washington, can conduct gene transfer experiments on up to 15 HIV seropositive patients undergoing allogeneic bone marrow transplantation for non-Hodgkin's lymphoma to evaluate the safety and efficacy of HIV-specific cytotoxic T lymphocyte (CTL) therapy. CTL will be transduced with a retroviral vector (HyTK) encoding a gene that is a fusion product of the hygromycin phosphotransferase gene (HPH) and the herpes virus thymidine kinase (HSV–TK) gene. The vector will deliver both a marker gene and a suicide gene in these T cell clones in the event that patients develop side effects as a consequence of CTL therapy. Data will be correlated over time, looking at multiple parameters of HIV disease activity. The objectives of these studies include evaluating the safety and toxicity of CTL therapy, determining the duration of *in vivo* survival of HIV-specific CTL clones, and determining if ganciclovir therapy can eradicate genetically modified, adoptively transferred CTL cells.

E. Amendment to Appendix D–XV of the NIH Guidelines

Appendix D–XV will read as follows:

Appendix D–XV

In addition to the conditions outlined in the initial approval, patients may be given a supplement of a CD–34+-enriched peripheral blood lymphoctyes (PBL) which have been placed in culture conditions that favor progenitor cell growth. This enriched population of cells will be transduced with the retroviral vector, G1NaSvAd. GINaSvAd is similiar to LASN, et distinguishable by PCR. LASN has been used to transduce peripheral blood T lymphocytes with the ADA gene. Lymphocytes and myeloid cells will be isolated from patients over time and assayed for the presence of the LASN or G1NaSvAd vectors. The primary objectives of this protocol are to transduce CD 34+ peripheral blood cells with the adenosine deaminase gene, administer these cells to patients, and determine if such cells can differentiate into lymphoid and myeloid cells *in vivo*. There is a potential for benefit to the patients in that these hematopoietic progenitor cells may survive longer, and divide to yield a broader range of gene-corrected cells.

F. Amendment to Introduction, Section II and V of the Points to Consider Regarding Review by the Human Gene Therapy Subcommittee; Amendment to Sections III–A and IV–C of the NIH Guidelines.

The following sections will be amended in the NIH Guidelines: Sections III–A, IV–C–1–b–(1), section IV–C–2, section IV–C–3–b–(1), section IV–C–3–b–(2)). The amended sections will read:

Section III–A. Experiments That Require RAC Review and NIH and IBC Approval Before Initiation.

Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH, the publication of the proposal in the Federal Register for 15 days of comment, review by the RAC, and specific approval by NIH. The containment conditions for such experiments will be recommended by the RAC and set by NIH at the time of approval. Such experiments also require * * *.

Section IV–C–1–b–(1). Major Actions. To execute major actions, the Director, NIH, must seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the agenda of the RAC meeting citing the major actions will be published in the Federal Register at least 15 days before the meeting, and the Director, NIH, will also publish the proposed actions in the Federal Register for comment at least 15 days before the meeting. In addition, the Director's proposed decision, at his/her discretion, may be published in the Federal Register for 15 days of comment before final action is taken. The Director's final decision * * *

Section IV–C–2. Recombinant DNA Advisory Committee. * * *. All meetings of the RAC will be announced in the **Federal Register**, including tentative agenda items, 15 days in advance of the meeting with final agendas, if modified, available at least 72 hours before the meeting. No item defined * * *.

Section IV–C–3–b–(1). Announcements of RAC meetings and agendas at least 15 days in advance; NOTE—If the agenda * * *.

Section IV–C–3–b–(2). Proposed major actions of the type falling under Section IV–C–1–b–(1) at least 15 days prior to the RAC meeting at which they will be considered; and

The following sections will be amended to the Points to Consider: Introduction, parts II, and V. This document was published in the **Federal Register** on March 1, 1990 (55 FR 7437), amended September 12, 1990 (55 FR 37565), and amended July 18, 1991 (56 FR 33174). The amended sections will read:

Introduction. (1) * * * RAC consideration of each proposal will be on a case-by-case basis and will follow publication of a precis of the proposal in the **Federal Register**, and an opportunity for public comment. RAC's recommendation on each proposal will be forwarded to the NIH Director for a decision which will then be published in the **Federal Register.**

Introduction. (4) * * * The IRB and IBC may, at their discretion, condition their approval on further specific deliberation by the RAC. Consideration of proposals by the RAC may proceed simultaneously with review by any other Federal agencies provided that the RAC is notified of the simultaneous review. Meetings of the RAC will be open to the public except where trade secrets or proprietary information would be disclosed. The committee * * *

Introduction. (6) * * * Part III summarized other requested documentation that will assist the RAC in their review of the proposals. Part IV specified reporting requirements.

Introduction. (7) The RAC will not at present entertain proposals for germ line alterations * * *.

Introduction. (9) In their evaluation of proposals involving the transfer of recombinant DNA into human subjects, the RAC will consider whether the design * * *. Accordingly, this document requests information that will enable the RAC to assess the possibility that the proposed experiments will inadvertently affect reproductive cells or lead to infection of other people (e.g., treatment of personnel or relatives).

Introduction. (10) In recognition of the social concern that surrounds the subject of gene transfer, the RAC will cooperate with other groups * * *.

Introduction. (12) * * * Investigators submitting proposals that employ essentially the same vector systems (or with minor variations), and/or that are based on the same preclinical testing as proposals previously reviewed by the RAC, may refer to preceding documents without having to rewrite such materials.

Part II. Special Issues. Although the following issues are beyond the normal purview of local IRBs, the RAC requests that the investigators respond to questions A and B below.

Part V. Minor Modifications. A minor change in a protocol approved by the RAC is a change that does not significantly alter the basic design of a protocol and that does not increase risk to the subjects. If the change has been approved by the relevant IRB and IBC, then the Chair of the RAC may give approval. It is expected that the Chair will consult with one or more members of the committee, as necessary. The Chair will report on any such approvals at the next regularly scheduled meeting of RAC.

I accept this recommendation to amend accordingly the NIH Guidelines in sections III–A and IV–C and to amend the Points to Consider in the Introduction, parts II, and V.

G. Amendment to Appendices B–I–B–1 and B–I–B–2 of the NIH Guidelines Regarding the Bacterial Order, Actinomycetales

Appendix B–I–B–1, Bacterial Agents, the following organisms will be added:

Amycolata autotrophica
Dermatophilus congolensis
Nocardia asteroides
Nocardia brasiliensis
Nocardia otitidiscaviarum
Nocardia transvalensis
Rhodococcus equi

Appendix B–I–B–2, Fungal Agents, the following organisms will be deleted:

"Actinomycetes (including Nocardia species, actinomyces species, and Arachnia propionica)[2]"

H. Amend Appendices B–I–C–1 and B–I–B–1 in the NIH Guidelines Regarding Mycobacterium Avium

Appendix B–I–C–1, Bacterial Agents, the following organism will be deleted:

Mycobacterium avium

Appendix B–I–B–1, Bacterial Agents, the following organism will be added:

Mycobacterium avium

OMB's Mandatory Information Requirements for Federal Assistance Program Announcements (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

EFFECTIVE DATE: April 17, 1992.

Bernadine Healy,

Director, National Institutes of Health.

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